Vitamin D Intoxication with Severe Hypercalcemia due to Manufacturing and Labeling Errors of Two Dietary Supplements Made in the United States

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Context: More than 50% of Americans use dietary supplements, and 60–70% fail to report this use to their physicians. Intoxication from vitamin D supplements has been rarely reported but may now occur more frequently. This may be attributable to an increase in vitamin D supplement intake due to the findings that deficiency is common and has been associated with a number of disease states.

Objective: We report two cases of vitamin D intoxication with dietary supplements made in the United States caused by manufacturing and labeling errors.

Methods: Case histories were obtained, and serial laboratory data (calcium and vitamin D metabolites) were measured. Each dietary supplement was analyzed by UV spectrophotometry followed by HPLC.

Results: In both cases, repetitive inquiries were required to elicit the use of dietary supplements. Because of significant manufacturer errors and a labeling error, patients had been consuming more than 1000 times the recommended daily dose of vitamin D_3. Hypercalcemia is directly proportional to serum 25-hydroxyvitamin D [25(OH)D] but not 1,25-dihydroxyvitamin D levels. It took approximately 1 yr to normalize 25(OH)D levels. However, once 25(OH)D levels decreased below 400 ng/ml, both patients became normocalcemic and asymptomatic without long-term sequelae.

Conclusions: Although rare, vitamin D intoxication should be considered in the differential diagnosis of hypercalcemia. Patients should be asked whether they are using dietary supplements, and serial questioning may be required because patients may not consider these supplements to be potential health risks. Errors in the manufacturing and labeling of dietary supplements made in the United States may place individuals at increased risks for side effects. (***J Clin Endocrinol Metab*** **96: 3603–3608, 2011)**

Fifty percent of Americans use dietary supplements, and many of them take more than one supplement (1, 2). Between 60 and 70% of patients fail to report the use of these supplements to their physicians (3). There has also been increasing interest by physicians in prescribing vitamin D supplements in particular for various illnesses (4). We present two cases of manufacturing and labeling errors of dietary supplements that caused vitamin D toxicity.

Subjects and Methods

Subjects

The patients were normocalcemic before hospital admission and had procured dietary supplements for the purpose of improving their overall health.

Clinical data and analysis of vitamin D metabolites

Case histories were delineated, and serial laboratory data were measured. 25-Hydroxyvitamin D [25(OH)D] was mea-

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Abbreviations: $1,25(OH)_2D$, 1,25-Dihydroxyvitamin D; 25(OH)D, 25-hydroxyvitamin D.

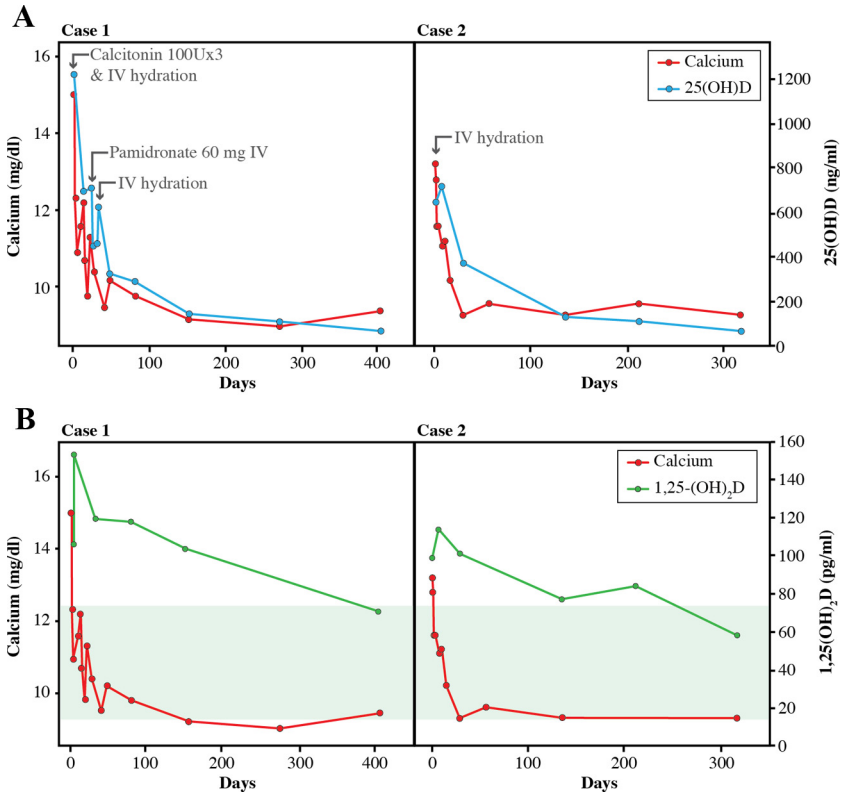

FIG. 1. A, Serum calcium levels and 25(OH)D over time. B, Serum calcium and $1,25(OH)_2D$ over time. *Shaded area* reflects normal range for $1,25(OH)_2D$.

sured by quantitative chemiluminescent immunoassay, and 1,25-dihydroxyvitamin D [$1,25(OH)_2D$] by RIA (ARUP Laboratories, Salt Lake City, UT).

Analysis of dietary supplements

Dietary supplements were analyzed for vitamin D content by dissolving in 100% ethanol; the concentration of vitamin D was then determined by UV spectrophotometry followed by HPLC (5).

Data analysis and statistics

Serum calcium, 25(OH)D, and $1,25(OH)_2D$ levels were plotted over time (Fig. 1). Regression analyses of calcium *vs.* 25(OH)D (Fig. 2A), calcium *vs.* creatinine (Fig. 2B), and calcium *vs.* $1,25(OH)_2D$ (Fig. 2C) were performed. A second-order polynomial function was fitted to the plot of 25(OH)D *vs.* $1,25(OH)_2D$ to estimate the correlation between them (Fig. 2D).

Case 1

In December 2009, a 58-yr-old man with no significant medical history presented with obtundation and a serum calcium of 15.0 mg/dl (3.75 mmol/liter). For the prior 3 wk, he had complained of fatigue, excessive thirst, polyuria, and poor mentation.

Admission laboratory values were significant for an elevated creatinine 1.78 mg/dl (135.7 μmol/liter) and mild anemia (hematocrit, 37.2%). Phosphorus, magnesium, and immunofixations of serum and urine were normal. PTH and parathyroid-related protein levels were undetectable. 25(OH)D was markedly increased to 1220 ng/ml (3.045 nmol/liter; normal range, 30–80 ng/ml). Liquid chromatography tandem mass spectroscopy detected only $25(OH)D_3$ with undetectable $25(OH)D_2$. $1,25(OH)_2D$ was 106 pg/ml (276 pmol/liter; normal range, 15–75pg/ml), with only $1,25(OH)_2D_3$ being detected. The 24-h urine calcium level was 499 mg (100–300 mg), and the urine calcium/creatinine ratio was 0.32 (<0.2 mg/mg). A renal sonogram revealed a mildly enlarged prostate and mild left hydronephrosis.

Initially, the patient had denied taking any medications. Upon repeated questioning, he admitted to taking multiple dietary supplements for 2 months, prescribed by physicians in the United Kingdom and California, respectively (Table 1). In addition, he was taking multiple hormones (Table 1), the serum levels of which were normal.

One of the supplements (vitamin and mineral Formula F; Table 1) was purported to contain 1600 IU (40 μg) vitamin D, 99% as D_3. Analysis by UV spectrophotometry and HPLC revealed that each capsule contained a significantly higher amount of 186,400 IU (4,660 μg) vitamin D_3. In addition to this manufacturing error, there was an error in labeling recommending 10 capsules instead of one capsule per day. Thus, the patient consumed 1,864,000 IU (46,600 μg) of vitamin D_3 daily for 2 months, more than 1,000 times what the manufacturer had led the patient to believe he was ingesting. Calcium levels normalized with iv treatment including normal saline, furosemide, and calcitonin (Fig. 1A).

After being discharged on oral hydration, a low-calcium diet, and no vitamin D-containing supplements, the patient was readmitted 1 wk later with a calcium level of 12.2 mg/dl (3.05 mmol/liter) and dehydration. Pamidronate 60 mg iv and iv hydration were prescribed. He was discharged after 7 d, again on low-calcium and no-vitamin D diet, but he required 1–2 liters of iv hydration at a local hospital every 4 d for 2 wk before the calcium level stabilized. It is useful clinically to note that calcium levels stabilized before normalization of 25(OH)D levels (Fig. 1A). 25(OH)D did not normalize until 13 months later, whereas $1,25(OH)_2D$ remained elevated for more than 1 yr (Fig. 1B). The patient was asymptomatic and remained normocalcemic after the 25(OH)D decreased below 400 ng/ml (1000 nmol/liter). Serum creatinine decreased to 0.94 mg/dl (83.1 μmol/liter) after 2 months of treatment. The prescribing homeopathic physician in the United Kingdom was notified on d 2 of the first hospitalization. He notified the company, which has since been liquidated, and vitamin and mineral Formula F was discontinued soon afterward.

Case 2

In January 2010, a 40-yr-old man with no significant medical history presented with nausea, vomiting, and a serum calcium of 13.2 mg/dl (3.3 mmol/liter). For the prior 2 wk he had complained of excessive thirst, polyuria, and muscle aches.

Laboratory values were significant for creatinine 2.0 g/d (152.5 μmol/liter), hematocrit 31.2%, and normal phosphorus, magnesium, immunofixation urine and serum, and renal sonogram. PTH intact and parathyroid-related protein levels were

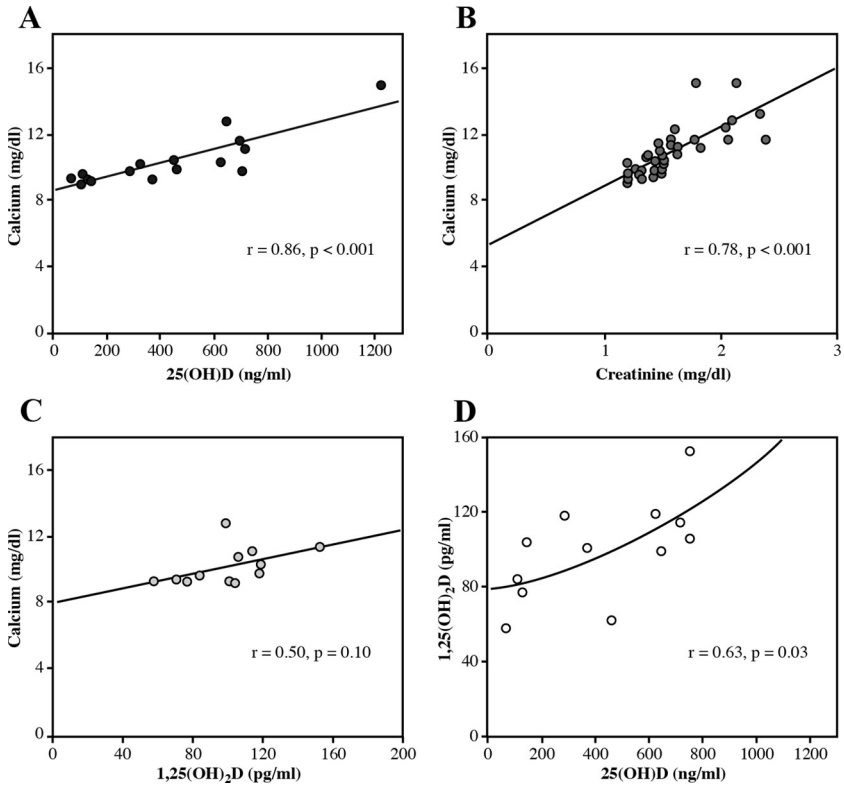

FIG. 2. Regression analysis of serum calcium *vs.* 25(OH)D (A), calcium *vs.* creatinine (B), and calcium *vs.* $1,25(OH)_2D$ (C), and 25(OH)D *vs.* $1,25(OH)_2D$ (D) in cases 1 and 2. D, A second-order polynomial function was fitted to the plot of 25(OH)D *vs.* $1,25(OH)_2D$ to obtain an estimate of the correlation between them.

undetectable. 25(OH)D was 645 ng/ml (1609.9 nmol/liter). Liquid chromatography tandem mass spectroscopy detected only $25(OH)D_3$, with undetectable $25(OH)D_2$. $1,25(OH)_2D$ was 99 pg/ml (257.4 pmol/liter), with only $1,25(OH)_2D_3$ being detected. The urine calcium/creatinine ratio was 0.36 mg/mg (<0.2 mg/mg).

After several inquiries, the patient admitted to taking multiple dietary supplements for 1 month purchased through the Internet. One of the supplements (Gary Null's Ultimate Power Meal; Triarco Industries, Wayne, NJ) was purported to contain 1000 IU (25 μg) of vitamin D_3 per daily dose. Analysis of this product by UV spectrophotometry followed by HPLC revealed a manufacturing error in which the daily recommended dose of two scoops actually contained 970,000 IU (24,300 μg) of vitamin D_3. Similarly, as in case 1, this manufacturing error resulted in a vitamin D content 1,000 times more than the label claimed.

Calcium levels normalized with iv hydration alone (Fig. 1A). The patient was discharged on oral hydration, a low-calcium diet, and no vitamin D-containing dietary supplements. He became asymptomatic after 1 month when the 25(OH)D decreased below 400 ng/ml (1000 nmol/liter). It took 10 months before the 25(OH)D normalized, whereas the $1,25(OH)_2D$ remained elevated for almost 1 yr (Fig. 1B).

Again, stabilization of calcium preceded vitamin D normalization. Renal function normalized 4 wk after the initial presentation. Regression analyses combining the data from both patients revealed that serum calcium levels were directly related to 25(OH)D and creatinine, but not $1,25(OH)_2D$ (Fig. 2, A–D).

The patient had ordered this supplement on the Internet where it is sold as a popular powdered meal. The error in manufacturing was alleged to be found in only one lot, which was then taken off the market.

Discussion

In the National Health and Nutrition Examination Survey (NHANES), 46–53% of adults reported taking dietary supplements (1, 2). The number of vitamin D-containing supplements sold in drugstores, health food stores, and on the Internet has recently increased (6–13). Sales of vitamin D supplements have doubled between 2009 and 2010, rising faster than those of any other supplements (14). This may be due to both the recently published NHANES data indicating that 41% of adults in the United States are vitamin D deficient with levels below 20 ng/ml (50 nmol/liter), as well as recent findings that vitamin D deficiency is related to many disease states (15–17).

Vitamin D intoxication has been reported only sporadically over the past several decades, but because of the recent increase in supplement use of vitamin D, it may be on the rise and should be included in the differential diagnosis of hypercalcemia (6–13, 18). The toxic dose of vitamin D is estimated to be greater than 100,000 IU (2,500 μg) per day for a duration of at least 1 month (19). Our patients had been taking 18 times (1,864,000 IU for case 1) and nine times (970,000 IU for case 2) the toxic dose. The management was more challenging in

TABLE 1. List of dietary supplements and hormone supplements in case 1

Dietary supplements	Hormonal supplements
Vitamin and mineral Formula F	GH (somatropin rDNA)
MVI and mineral	Adrenex 100 mg/2 mg (L-dopa/phenylalanine)
Milk thistle with kelp	T_3/T_4 10/30 μg
Vitamin B complex plus vitamin C	T_3 15 μg
Magnesium 40 mg, elemental food	Progesterone 100 mg Pregnenolone 400 mg Melatonin 1 mg Amino blend (carnosine, alanine, arginine, glutamine, *etc.*)

case 1 than in case 2 because the daily dose was twice as much and the duration of intake had been longer.

The signs and symptoms of hypercalcemia are the most prominent clinical manifestations of vitamin D toxicity. Our patients exhibited the common symptoms of nausea, polyuria, increased thirst, fatigue, and poor mentation, and the reversible findings of mild normocytic anemia and renal impairment that is frequently seen with vitamin D intoxication (20, 21). Serum creatinine was directly related to serum calcium levels (Fig. 2). Hypercalcemia is known to induce a reversible renal insufficiency via decreased glomerular filtration rate due to renal vasoconstriction (22).

To our knowledge, there has only been one prior report in which 25(OH)D exceeded 1000 ng/ml (2500 nmol/liter) (13) (Table 2). Because vitamin D is fat-soluble and 25(OH)D has a half-life of 2–3 wk, vitamin D toxicity usually takes weeks to months to normalize. In our severely toxic patients, it took approximately 1 yr for 25(OH)D levels to return to normal. However, the patients became normocalcemic and asymptomatic once the 25(OH)D levels fell to less than 400 ng/ml (1000 nmol/liter). This important clinical finding is consistent with a prior observation by Koutkia *et al.* (10), as well as an *in vivo* study by Deluca *et al.* (23).

Vitamin D toxicity is treated mainly by managing the resultant hypercalcemia with aggressive hydration and low dietary calcium/vitamin D intake. Calcitonin may be

TABLE 2. Summary of previous reported cases of vitamin D intoxication due to food products or dietary supplements

First author, year (Ref.)	Source of vitamin D	Vitamin D (IU/ml)	25(OH)D (ng/ml)	25(OH)D (nmol/liter)	Treatment	Follow-up	Complications
Down, 1979 (6)	Nut oil from United Kingdom	55			Steroids, neutral phosphate	9 yr	Nephrocalcinosis
		60			Steroids, neutral phosphate		
		9.6			Steroids, neutral phosphate		
Jacobus, 1992 (7)	Milk from United States		310	774			
			665	1660			
			203	507			
			360	899			
			83	207			
			270	674			
			169	424			
			280	699			
Koutkia, 2001 (10)	Dietary supplement from Canada		487	1216	IV hydration	30 months	
Vieth, 2002 (13)	Table sugar from Canada		1482[a]	3700	IV fluids, steroids, Na phosphate, bisphosphonates	2 yr	
Klontz, 2007 (9)	Dietary supplement from United States		469	1171	IV hydration, pamidronate, Lasix	10 months	Death from unknown cause
Leu, 2008 (11)	Dietary supplement from Dominican Republic		150	374	IV hydration, Lasix, pamidronate	4 months	
Kaptein, 2010 (8)	Dietary supplement from The Netherlands		550	1372	IV hydration, bisphosphonates, Lasix	6 months	Epilepsy
	Dietary supplement from The Netherlands		258	644	IV hydration, pamidronate	4 wk	
Lowe, 2010 (12)	Dietary supplement from Dominican Republic		288	719	IV hydration, bisphosphonates		
			525	1310	IV fluids, steroids		
			94	235			
			370	924			
			295	736			
			184	459			
			154	384			
			119	297			
			194	484			

[a] Only case in which 25(OH)D exceeded 1000 ng/ml (2500 nmol/liter).

used in the acute setting. In severe cases, such as case 1, corticosteroids or bisphosphonates have been prescribed as well. In two small studies, corticosteroid and pamidronate were equally effective in reducing the plasma calcium concentration, although pamidronate did so more quickly (12, 24).

In vitamin D intoxication, *in vivo* data reveal that 25(OH)D, rather than $1,25(OH)_2D$, is responsible for toxicity because supraphysiological concentrations of 25(OH)D can bind the vitamin D receptor and induce transcription of several target genes and suppress renal CYP27B1 (23). Our data show that 25(OH)D decreases over time, whereas $1,25(OH)_2D$ levels were maintained in a narrower range (Fig. 1B). We also found that serum calcium levels were directly related to serum 25(OH)D, but not to $1,25(OH)_2D$ (Fig. 2). These data support the recommendation to assess serum 25(OH)D and not $1,25(OH)_2D$ to determine clinical status (16).

In a few large analyses, up to 70% of patients do not report the use of alternative treatments to their physicians (3). Many individuals take more than one dietary supplement. People are commonly unaware of the potential toxicity or side effects of these supplements. Therefore, it is critical that practitioners routinely and thoroughly inquire about dietary supplement use. These two cases illustrate these points and that repeated questioning may be necessary. Physicians may need to be specifically trained in eliciting a history of dietary supplement intake (25).

Errors in manufacturing and labeling of dietary supplements may place individuals at increased risks for side effects. Because of these errors, our patients were taking 1000 times more than the alleged amount of vitamin D in two U.S. dietary supplements. Although vitamin D intoxication has been associated with food products in the United States (7) and in supplements from other countries (8, 10–12), we found only one other case attributable to a U.S. manufactured supplement (13) (Table 2).

In the Dietary Supplement Health and Education Act of 1994, dietary supplements are considered foods, not drugs. Although the Food and Drug Administration (FDA) cannot oversee the manufacturing of these supplements, they have established a web-based reporting site for adverse events via Med Watch. However, reporting through this site happens in less than 1% of cases (26), and therefore the magnitude of the problem is greater than its official documentation. The FDA has also launched a voluntary program for dietary supplement companies to verify their products. Verified products are recognized with a U.S. Pharmacopeia (USP) seal on their label. Neither supplement in our two cases was USP labeled.

In summary, these two cases of severe hypercalcemia due to vitamin D toxicity from dietary supplements highlight several issues. Many people take more than one supplement, and most do not report this to their physicians. Thorough and directed history is critical for early diagnosis because laboratory results can be delayed by days. Once detected, vitamin D intoxication can be managed effectively and usually does not appear to cause long-term sequelae. Hypercalcemia resolves months before normalization of serum 25(OH)D levels. Errors in manufacturing and labeling place individuals at risk for side effects of dietary supplements. We speculate that greater manufacturer participation in the USP program, increased physician reporting on Med Watch, and increased FDA oversight of the production and labeling of dietary supplements may prevent unnecessary and dangerous toxicities.

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